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High-dose antipsychotic medication

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The dopamine hypothesis for the mode of action of antipsychotic drugs has been with us for some 30 years and has, by and large, withstood the test of time. It simply states that antipsychotic drugs owe their therapeutic effects to an ability to block central dopamine receptors. This has given us a working and testable explanation for the effects of these drugs and it has prompted the synthesis of new agents. While so-called antipsychotic drugs (otherwise known as neuroleptics or major tranquillisers) are known to be effective in schizophrenia and related psychoses, mania, and the agitation associated with severe depressive illness or organic disorder, this paper is only concerned with the pharmacotherapy of schizophrenia.

Expose the brains of patients suffering from schizophrenic illness to a D_2 dopamine receptor blocker, and in 7 cases out of 10 there will be a useful amelioration of positive psychotic symptoms, usually within two months.

What do we do about the 3 out of 10 who do not get better? Most clinicians edge the dose of antipsychotic medication up – sometimes past the point at which Parkinsonian signs become prominent, and usually within the dose maxima specified in the product licence as reproduced in the published ABPI Data Sheet Compendium and largely reflected in the *British National Formulary* (BNF) (Table 1). That would seem reasonable as a strategy to take account of individual differences in absorption, metabolism and elimination. However, still faced with therapeutic failure, the clinician sometimes pushes the dose further, into the realm of high-dose or 'mega-dose' therapy. Terminology here is loose, but the term 'high dose' is probably applicable at daily doses greater than 1000 mg chlorpromazine or 100 mg haloperidol, or equivalent (see Table 1), and the term 'conventional dose' will be used here to mean doses lower than these. It must be remembered that the pharmacological effect of more than one antipsychotic agent should be considered to be additive. Thus, in calculating whether or not the patient's medication should be considered 'high dose', the combined daily dose (expressed in mg equivalents) should be worked out.

Table 1. *Advisory maximum daily oral doses from the British National Formulary*

Drug	Dose: mg
Sulpiride	2400
Chlorpromazine	1000
Clozapine	900
Thioridazine	800
Remoxipride	600
Loxapine	250
Droperidol	120
Haloperidol	100 (occasionally 200)
Pimozide	20
Risperidone	16*

*Product licence / data sheet.

Clinicians are commonly faced with patients suffering from schizophrenia who do not respond to conventional doses of antipsychotic drugs. Given that the upper dose limits specified in the data sheets and BNF have been chosen from available evidence on the risks and benefits, the clinician embarking on doses higher than these would do well to consider whether the benefits outweigh the possible risks and whether preferable alternatives exist. Before considering the issues relevant to these questions, it is necessary to have a working understanding of the current view on the mode of action and clinical use of antipsychotic drugs.

Mechanism of action

The dopamine hypothesis was derived largely from observations which we now know relate to one subtype of dopamine receptor, the D_2 receptor. This receptor is found in all brain areas to which dopamine-containing neurons project. They are

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Box 1. Doctors contemplating the use of high-dose antipsychotic drugs should ask themselves the following questions:

1 Are high doses effective?
2 What are the dangers?
3 What is the pharmacological rationale?
4 What are the alternatives?

richest in 'striatal' areas such as caudate and putamen, and are also found in mesolimbic areas such as the amygdala, nucleus accumbens, cingulate, and prefrontal cortex. It has been assumed that antipsychotic effects are mediated through actions at dopamine receptors in limbic areas.

All known antipsychotic drugs are antagonists at D_2 receptors, but their selectivity and potency vary considerably. By 'selectivity' is meant the 'cleanliness' of their pharmacology – what receptors other than D_2 receptors the drug might block.

'Potency' is a complex property, reflecting the bioavailability of the drug at strategic sites, and the affinity of the drug for the receptor; a drug with a high affinity will occupy a high percentage of receptors at relatively low drug concentration.

Antagonism at D_2 receptors is responsible for extrapyramidal side-effects and hyperprolactinaemia. Inference about the degree of D_2 receptor block in the basal ganglia from clinical extrapyramidal signs is complicated by the fact that coincidental blockade at acetylcholine and/or serotonin receptors will minimise or abolish the motor effects of D_2 block.

Other side-effects, such as sedation, postural hypotension, dry mouth, cardiotoxicity, and so on, are a result of the ability of many, if not most, antipsychotic drugs to act as antagonists at receptors other than D_2 and to affect membrane channels for ions such as sodium and calcium. For example, H_1 and α_1 noradrenaline blockade may be associated with sedation and (in the latter case) with hypotension; acetylcholine receptor block is associated with dry mouth and other atropinic effects, and ion channel block may be the cause of disturbance in excitable tissue such as the myocardium.

To what extent the other receptor actions contribute to the antipsychotic effect originally credited to D_2 receptors remains a matter of fierce debate. The dopamine receptor family has now grown to comprise five clearly defined subtypes (D_{1-5}). Data on effects at D_2 receptors are by far the most plentiful, but information is growing on the action of antipsychotics at other dopamine receptors, notably D_3 and D_4, which appear to be particularly enriched in mesolimbic areas of the brain.

Clinical use of antipsychotics

The place of these agents is based predominantly on their ability to ameliorate the positive symptoms of schizophrenic illness, with associated behavioural improvement. A beneficial effect on negative symptoms is much less dependable. A fair degree of success is achieved in approximately 70% of patients suffering from schizophrenic illness, with benefits usually evident on diagnostic psychotic features within four to eight weeks.

However, antipsychotic drugs are also used routinely for a much less specific purpose: the control of disturbing and/or dangerous behaviour in the acutely psychotic patient. This effect is often sought in emergencies and during the early stages of treatment, before the onset of the truly antipsychotic action. Such behavioural control is often achieved only with accompanying sedation and possibly extrapyramidal impairment. (Sedation is not confined to antipsychotic drugs, as reduced arousal is a marked effect of benzodiazepines.)

Resort to high doses can occur in clinical situations of essentially two sorts:

(1) the subacute or chronic failure of the patient to experience any reduction in core psychotic symptoms
(2) the failure of conventional doses to ameliorate disturbing or dangerous behaviour.

While the issues considered below are relevant mainly to the problem of chronic treatment resistance, the principles also apply, to some extent, to the need for behavioural control.

Efficacy of high doses

There is no published evidence for the efficacy of high-dose medication as a generally effective strategy either to accelerate therapeutic response or to increase the number of patients who respond satisfactorily to medication. Nor is there any evidence that escalating doses produce a response in chronically resistant patients (Kane, 1994).

Systematic studies of high-dose antipsychotics tend, naturally, to draw conclusions from averages, which may fail to reveal statistically significant

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differences while obscuring perhaps dramatic individual responses. Studies on treatment-resistant patients tend to involve small samples, and this could lead to 'type 2' statistical errors, through which differences are missed.

Despite the lack of support from the literature, there is a belief among clinicians that high doses may evoke a response where conventional doses have failed; this belief probably owes more to anecdotal experience than systematic study – we all tend to remember the occasional patient who did respond to high doses.

Why worry? The dangers of high dose

Sudden deaths

The possibility that antipsychotic drugs, especially when used at higher than conventional doses, may be associated with sudden death has excited interest and concern within the media. It is a concern shared by the Royal College of Psychiatrists and the Committee on the Safety of Medicines, and definitive studies are being mounted in the UK to examine the issue. Unexpected, probably cardiac, deaths have been reported in psychiatric units (Simpson *et al*, 1987; Mehtonen *et al*, 1991) for which antipsychotic drugs have been blamed. In the latter study, from Finland, sudden deaths were associated with so-called low-potency drugs, such as the phenothiazines. It has been said that as many as 50 sudden deaths per year may be occurring in the UK among patients on antipsychotic drugs, but the precise figure and the identification of a causal link must await further study.

Suspicion is justified, since pharmacologically plausible mechanisms can be suggested for such a danger. The ability of some antipsychotics to produce profound hypotension has long been known, and probably relates to antagonism at noradrenaline receptors peripherally. A more sinister and covert action at sodium and calcium channels may result in severe cardiac dysrhythmias, even at conventional doses. Such effects may underlie the prolongation of the Q–T interval on electroencephalography, which has been reported with pimozide, and may also produce T wave changes and *torsades des pointes*.

Ion channel effects are particularly relevant to the question of high-dose medication since, unlike occupancy of transmitter receptors, effects at ion channels are effectively non-saturable; the higher the concentration of drug to which tissue is exposed, the higher the percentage of channels affected.

Box 2. Dangers of high doses

Sudden death (through hypotension or cardiac dysrhythmia)
Severe extrapyramidal impairment
Neuroleptic malignant syndrome (related to rate of dose escalation)
'Paradoxical' deterioration of behaviour

Extrapyramidal disorder

High dosing is associated with severe Parkinsonism and akathisia, but dystonias are less clearly dose related. Excessive dosing may even raise the probability of tardive dyskinesia.

Neuroleptic malignant syndrome

The risk of this potentially lethal syndrome is probably more closely related to the rate of dose escalation rather than the size of the dose *per se*.

Paradoxical/violent behaviour

Barnes & Bridges (1980) have reported the emergence of 'paradoxical' disordered behaviour in patients as the dose of antipsychotic rises. Severe akathisia may be expressed as a dramatic disturbance of behaviour. High doses of drugs with atropinic effects (such as thioridazine) may cause toxic confusional states due to blockade of central acetylcholine receptors.

It has also been suggested (Hirsch & Barnes, 1994) that a danger exists of 'withdrawal' rebound in behavioural disturbance during dose reduction following high doses.

What rationale for high dose?

Despite the absence of firm evidence for efficacy and in the light of very real dangers, the case for the occasional use of high-dose medication in selected patients might be supportable if some *a priori* pharmacological justification could be provided.

It is well established that systemic concentrations of antipsychotic drugs, and in some cases active metabolites, vary considerably between people on the same oral dose. This variation probably arises out of differences in compliance, in first-pass metabolism (enzymatic breakdown in gut wall and liver), and in elimination. In most patients there is some sign

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Box 3. Do high doses make any pharmacological sense?

Suggestion	*Verdict*
More complete D_2 receptor block	Unlikely
Block of D_2 receptors in inaccessible but important sites	Unlikely
Block of receptors other than D_2	Possible

or symptom signifying entry of pharmacologically active amounts of drug into the brain – be it extrapyramidal disorder or sedation – before the conventional dose ceiling is reached.

In the absence of any effect whatsoever within the conventional dose range, it may be reasonable to suspect a problem of absorption or elimination and to increase the dose until some effect on the central nervous system appears. If impaired oral bioavailability is suspected, or even non-compliance, then a trial of intramuscular medication might be considered (such as the relatively short-acting depot preparation, zuclopenthixol acetate). For those with access to such assays, measurement of plasma drug concentrations may provide a crude check on compliance and bioavailability.

Assuming that pharmacologically active concentrations of drug are being achieved in the systemic circulation (and this is likely in the vast majority of compliant patients within the conventional dose range), then there remain three theoretical justifications for high-dose exposure in resistant psychosis:

(1) conventional doses have not blocked a sufficient proportion of D_2 receptors generally in the brain
(2) conventional doses have not blocked D_2 receptors in the right place
(3) blockade at receptors *other* than D_2 is progressively recruited as the drug concentration rises, implying a lower affinity of the drug for other receptors which might contribute to the psychosis.

Incomplete D_2 block?

Until recently it has not been possible to do anything other than guess at the percentage of D_2 receptors which might be blocked anywhere in the human brain at conventional doses of antipsychotic. An educated guess could have been made from the work of Hornykiewicz and his colleagues, who showed, from clinicopathological deduction, that neurological signs appear in Parkinson's disease only after some 80% of dopamine cells are lost from the substantia nigra. A crude extrapolation might suggest, therefore, that some 80% of dopamine receptors might have to be blocked before Parkinsonian signs appear with antipsychotic medication.

This crude guess has been largely borne out by work using sophisticated isotope imaging techniques such as positron emission tomography (PET). Work, mainly from the Karolinska Institute, has shown the degree of D_2 block in the putamen of patients exposed to antipsychotic drugs. Parkinsonian signs were apparent in patients once 75–80% of D_2 receptors were blocked, and this happened in the majority of patients at doses of haloperidol below 15 mg per day (Farde *et al*, 1992). This is a most important reference point, since it means that substantial D_2 block is occurring on average at a dose some six times lower than the BNF ceiling.

Earlier studies had also suggested that over 80% of D_2 receptors are usually blocked well within the conventional dose range (Farde *et al*, 1988). A curvilinear relationship between drug occupancy and drug concentration is evident, revealing that a very shallow part of the curve relating receptor occupancy to drug concentration is reached at around 80% receptor occupancy. Increases in drug dose thereafter appear to have a rapidly decreasing incremental effect on receptor block.

The conclusion of Farde *et al*, that past a certain point increased doses achieve little extra D_2 receptor block, has been confirmed by Wolkin *et al* (1989*a*). Wolkin went further to explore with PET D_2 receptor block in responders and non-responders to haloperidol. No difference in occupancy was found (Wolkin *et al*, 1989*b*).

Thus, overall, no support is evident from work on the basal ganglia for the use of high dose on the basis of blocking more D_2 receptors.

D_2 receptors in strategic areas?

For increasing dose to produce D_2 block in certain brain areas, it must be postulated either that a barrier to drug distribution exists in some brain areas, or that D_2 receptors in, say, limbic fields have a lower affinity for antipsychotic drugs than in basal ganglia. Neither possibility seems likely. No site-specific barriers have been found for these drugs, and in any case antipsychotic drugs are highly lipid soluble.

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Differential affinity between brain sites also appears unlikely; Leysen and colleagues have investigated the differential affinity of haloperidol and risperidone for limbic and striatal areas of mammalian brain *ex vivo*, and have found that the affinity of each drug for D_2 receptors in limbic areas is almost identical to its affinity in striatum (Schotte *et al*, 1993).

Increasing the dose above conventional limits seems unlikely to reach D_2 receptors in more useful places.

Non-D_2 receptors

It is possible that in some patients the neurochemical expression of schizophrenic illness is different from that in the majority; perhaps for these patients D_2 block is insufficient (or even unnecessary) to achieve a therapeutic response. Maybe in this minority the dopamine hypothesis does not hold.

By increasing the dose are we recruiting blockade at receptors other than D_2? The answer is probably yes, but many candidates exist (Box 4).

Most antipsychotic drugs have a lower affinity at receptors other than D_2, but this is not the case for the currently popular 'atypical' antipsychotics. Much attention has recently been directed at the affinity of antipsychotic drugs for 5-HT_2 and D_4 receptors.

To visualise what happens when the dose of a drug is systematically increased, we have to be aware of the receptor profile of the drug – an image of the rank order of receptor affinities, or, in other words, which new receptors start to be blocked as the dose rises. Fig. 1 represents a semi-quantitative attempt to draw dose–occupancy profiles for a small range of popular antipsychotic agents. These profiles might be seen as the receptor signature for each antipsychotic, and it can be seen that each signature is different.

A clinical reference point is the dose at which Parkinsonian signs appear – at that dose some 80% of D_2 receptors are likely to be blocked (Farde *et al*, 1992), although this inference is not possible with drugs having strong anticholinergic or anti-serotonergic actions. The prototype antipsychotic, chlorpromazine, is remarkable for the range of receptors it blocks within a tight dose range (Fig. 1). Thioridazine has a similar broad spectrum of action within a few dose multiples, in contrast to sulpiride, pimozide or haloperidol, which are relatively selective (Fig. 1). Clozapine, the prototype atypical neuroleptic, is distinguished by its relatively low affinity for D_2 receptors and remarkably high affinity for H_1, 5-HT_2, D_4 and α_1 noradrenaline receptors. Risperidone, a recently marketed atypical, has extremely high affinity for 5-HT_2 and α_1 noradrenaline receptors, and also a high affinity for D_2 receptors (Fig. 1).

Box 4. Receptors most commonly associated with antipsychotic drug action

Dopamine
- **D_1**
- **D_2**
- **D_3**
- **D_4**
- **D_5**

Noradrenaline α_1
Histamine H_1
Serotonin 5-HT_2
Acetylcholine (muscarinic) ACh_m

Examination of these profiles can lead to many provisional deductions and suggestions, but some general conclusions might be permissible in relation to the use of high doses:

(1) high-dose medication is probably not required for substantial blockade of D_2 receptors
(2) high doses are not required for blockade of any of the receptor types shown in the figures; by selecting a particular antipsychotic according to its receptor profile, receptor block can be achieved within conventional dose ranges.

D_4 receptors

D_4 receptors have caused excitement through the publication by Seeman *et al* (1993) which reports a sixfold increase in the density of D_4 receptors in post-mortem brain tissue from schizophrenic patients compared with various controls. If D_4 is the unwitting target at which antipsychotic medication is aimed, then sulpiride, thioridazine or clozapine should all be particularly effective drugs. While a special place for clozapine has been identified in the treatment of resistant schizophrenic illness (Kane *et al*, 1988; Baldessarini & Frankenburg, 1991) this has not yet been shown to be the case with other drugs capable of blocking D_4 receptors. Suggestions have similarly been made that atypical agents may be particularly effective because they block 5-HT_2 or D_1 receptors. However, as can be seen from Fig. 1, chlorpromazine has a relatively high affinity for both 5-HT_2 and D_1 receptors.

Other types of blockade

Sadly, these inconsistencies prompt yet another two suggestions which might accommodate a pharmacological justification for the use of high doses in resistant cases.

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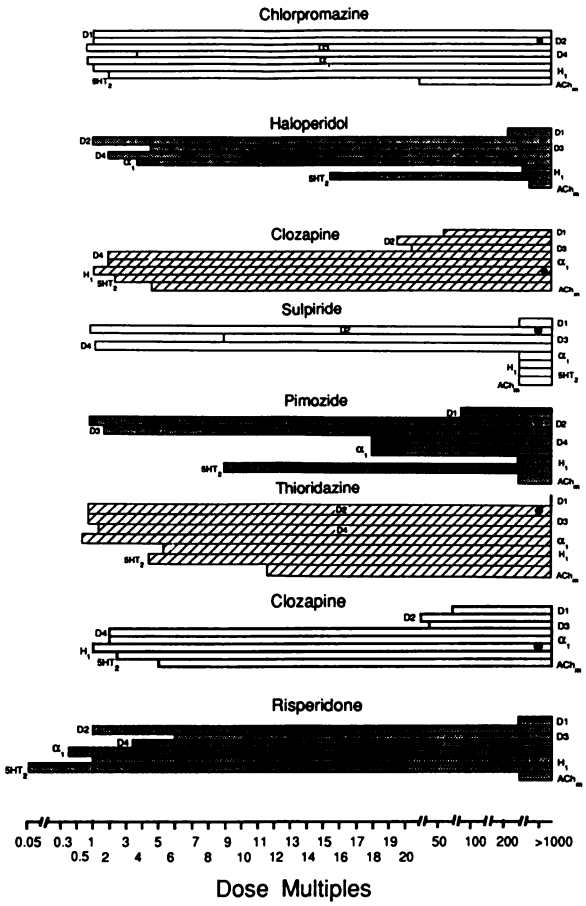

'Dose multiples' are derived simply and directly from the average rank order of affinities for the various receptor types. The horizontal bars, one for each receptor type (respectively D_1, D_2, D_3, D_4, α_1, H_1, 5-HT_2 and ACh_m for each drug) illustrate relative receptor occupancy by a drug as its concentration rises. This simplified illustration was derived from various sources of published data. Within each published data set the affinity constant for each drug at each receptor type was expressed as a whole-number ratio to its affinity at the D_2 receptor (●). This number was taken as the potency ratio among receptors for that drug. In the case of clozapine, the reference affinity (●) was for the H_1 receptor, for which clozapine has highest affinity. For each drug, these ratios for various receptors were averaged between published data sets and the result is a number of average potency ratios calculated from the following literature sources: Schotte *et al* (1993); Sokoloff *et al* (1990); Leysen & Niemegeers (1985); Seeman (1990); Reynolds (1992); Van Tol *et al* (1991); Leysen *et al* (1992*a*,*b*); Leysen (1993); Snyder *et al* (1974).

Fig. 1. Dose–occupancy profiles of some popular antipsychotic drugs

First, it may be that in some patients the therapeutic response is not related specifically to blockade at any one receptor type, but rather to the pattern of blockade at a whole series of receptors. It has been established that complex 'cross-talk' takes place between receptors within the neuronal membrane, and the net effect on neuronal excitability will

Box 5. High doses are not necessary to block any of the individual receptors currently felt to be important in the therapeutic action of antipsychotic drugs.

derive from a combination of effects at various receptor types which will vary in both intensity and quality. Although perhaps unlikely, the wrong signature may be converted into the correct one by escalating the dose. Understanding such an effect might be possible with the use of drug receptor profiles such as those shown in Fig. 1, but would undoubtedly require a level of sophistication in our knowledge and application of synaptic pharmacology which is far beyond the present position.

The second and perhaps associated possibility, that high doses may allow the drugs to occupy receptors of which we are ignorant (either unknown types or known receptors with subtle changes associated with the psychotic trait), is clearly impossible to test at present.

Conclusions

From the available evidence on receptor affinities, it would appear that any of the commonly researched receptors can be blocked by the use of conventional doses of a particular drug, or modest combination of drugs. The lack of any pharmacological rationale for the use of high dose is entirely consistent with the lack of published evidence for clinical efficacy. It must be stressed, however, that these must be treated as no more than provisional conclusions. Failure to secure a therapeutic response with conventional doses in some patients undoubtedly reflects our ignorance of the neurochemical processes involved. Until we understand the reason for this failure, the use of high doses, with a low probability of success, must be approached with due caution. What is quite clear is that escalating doses run the risk of more serious side-effects, regardless of the drug, and perhaps the most dangerous are those caused by interference with ion channels in the heart.

For an excellent summary of the clinical alternatives to the use of high dose in refractory patients and the safeguards which should be taken if high dose is contemplated, the reader is referred to the consensus statement from the Royal College of Psychiatrists (Thompson, 1994).

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Multiple choice questions

1 The following daily oral doses of antipsychotic drugs (mg) are the advisory maxima stipulated in the BNF:
- a chlorpromazine 1000
- b haloperidol 100 (occasionally 300)
- c pimozide 30
- d droperidol 120
- e thioridazine 1200
- f clozapine 900

2 High-dose antipsychotic medication:
- a should be tried in any patient who has not responded to conventional doses within 3 weeks
- b has proven efficacy in a subset of schizophrenic patients
- c is never warranted
- d is a recognised cause of death

3 Reasons for failure to respond to antipsychotic medication include:
- a non-compliance
- b malabsorption
- c inaccessibility of limbic brain areas
- d individual differences in the neurochemical expression of schizophrenia

MCQ answers

1	
a	T
b	F
c	F
d	T
e	F
f	T

2	
a	F
b	F
c	F
d	F

3	
a	T
b	T
c	F
d	T

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